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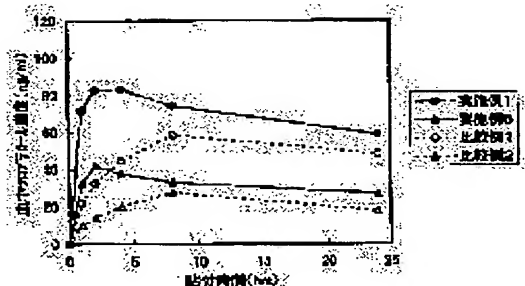
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(54) PERCUTANEOLIS ABSORPTION TYPE PREPARATION

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain the subject preparation having excellent skin adhesiveness, initial absorption of tulobuterol and durability of effective concentration in blood, by adding a specific amount or more of tulobuterol in a dissolved state to a paste layer.

SOLUTION: This preparation is obtained by laminating a paste layer containing tulobuterol and a tacky agent such as preferably an acrylic tacky agent, a rubber-based tacky agent or the like to a substrate and adding ≥ 5 wt.%, preferably ≥ 10 wt.% of tulobuterol in a dissolved state to the paste layer.



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CLAIMS

[Claim(s)]

[Claim 1] Percutaneous absorption mold pharmaceutical preparation which the plaster body layer containing tulobuterol and a binder is the percutaneous absorption mold pharmaceutical preparation which comes to carry out a laminating to a base material, and is characterized by tulobuterol containing 5% of the weight or more in the state of the dissolution in this plaster body layer.

[Claim 2] Percutaneous absorption mold pharmaceutical preparation according to claim 1 whose binder is characterized by being an acrylic binder or a rubber system binder.

[Claim 3] Percutaneous absorption mold pharmaceutical preparation according to claim 2 characterized by containing the polymer with which an acrylic binder comes to carry out the polymerization of the acrylic-acid alkyl ester whose carbon numbers of an alkyl group are 4-12 (meta) at 50% of the weight or more of a rate.

[Claim 4] Percutaneous absorption mold pharmaceutical preparation according to claim 2 characterized by containing the copolymer with which an acrylic binder comes to copolymerize the functionality monomer which has acrylic-acid alkyl ester whose carbon numbers of an alkyl group are 4-12 (meta) 60 to 98% of the weight, and has at least one partial saturation double bond in intramolecular, and has a functional group in a side chain at 2 - 40% of the weight of a rate.

[Claim 5] Percutaneous absorption mold pharmaceutical preparation according to claim 4 characterized by being the radical chosen from the group which the functional group of a functionality monomer becomes from a carboxyl group, hydroxyl, a sulfonic group, the amino group, an amide group, an alkoxyl group, a cyano group, and an acyloxy radical.

[Claim 6] Percutaneous absorption mold pharmaceutical preparation according to claim 4 characterized by being the monomer chosen from the group which a functionality monomer becomes from acrylic-acid (meta) and acrylic-acid (meta) 2-hydroxyethyl ester, a styrene sulfonic acid, acrylamide (meta), vinyl pyrrolidone, acrylic-acid (meta) 2-aminoethyl ester, acrylonitrile, acrylic-acid (meta) 2-methoxy ethyl ester, and vinyl acetate.

[Claim 7] Percutaneous absorption mold pharmaceutical preparation according to claim 2 characterized by a rubber system binder containing at least a kind of macromolecule chosen from a polyisobutylene and a styrene diene styrene block copolymer.

[Claim 8] Percutaneous absorption mold pharmaceutical preparation according to claim 1 to 7 characterized by containing at least a kind of additive chosen from the group which consists of polyoxyethylene alkyl ether with the ester of the fatty acid of carbon numbers 12-16, the monoglyceride of the fatty acid of carbon numbers 8-10, the ester of the dibasic acid of carbon numbers 6-10, and 2-5 addition mols, and polyoxyethylene alkyl phenyl ether with 2-5 addition mols further into a plaster body layer five to 50% of the weight.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Field of the Invention] It relates to the percutaneous absorption mold pharmaceutical preparation which is excellent in the initial absorptivity of tulobuterol, and the durability of effective blood drug concentration while it is excellent in a skin adhesive property, when this invention is stuck on a hide skin surface in detail about the percutaneous absorption mold pharmaceutical preparation for sticking on a hide skin surface and prescribing tulobuterol for the patient continuously from the skin to the living body.

[0002]

[Description of the Prior Art] Tulobuterol is beta 2 of the sympathetic nerve. It has a bronchodilator action by stimulating an acceptor alternatively, and is widely used for the therapy of the chronic bronchitis, bronchial asthma, etc. for the purpose of mitigation of the dyspnea of the patient who started a respiratory stenosis.

[0003] As an approach of prescribing tulobuterol for the patient in the living body, although there are, generally the administering methods, such as a tablet, there are problems, such as a manifestation of the side effect accompanying the difficulty of the administration to a child etc. and the rapid rise of drug blood drug concentration and lack of the durability of drug effect. Then, in order to solve these problems, the percutaneous absorption mold pharmaceutical preparation for prescribing a drug for the patient through a hide skin surface to the living body in recent years is developed about various drugs. In JP,5-194202,A (LTS roman), JP,5-238953,A (Zhang Bon), JP,7-285854,A (NITTO DENKO), JP,7-25669,B (NITTO DENKO), etc., percutaneous absorption mold pharmaceutical preparation is proposed also about tulobuterol.

[0004] These proposals are the pharmaceutical preparation which contained the tulobuterol more than the saturation solubility to a binder in the plaster body layer, and a part of tulobuterol mainly distributed by the crystallized state in the plaster body layer. It is thought that the durability of drugs emission increases, so that the percutaneous absorption rate of drugs increases, so that drugs are generally dissolved by high concentration into a plaster body layer, and drugs are made to contain in a high content in a plaster body layer. However, it is difficult to carry out dissolution maintenance of the drugs stably by high concentration in the polymer generally used for a plaster body layer, and in order to satisfy both the percutaneous absorption rate of drugs, and the durability of emission, the method of making drugs contain by the high concentration more than saturation solubility in a plaster body layer as indicated in the above-mentioned precedence official report, and holding some drugs in a plaster body layer by the crystallized state is used.

[0005]

[Problem(s) to be Solved by the Invention] However, a drugs crystal will tend to deposit in the plaster body layer interface (front face) to which the pharmaceutical preparation with which the drugs crystal which is a solid-state exists in a plaster body layer contacts the skin, and the skin adhesive property of pharmaceutical preparation will fall. moreover, it is expected that the skin adhesive property of pharmaceutical preparation and drugs emission nature change with time because the diffusion rate of the drugs molecule in the inside of a polymer is markedly alike from it in a liquid, a deposit of a drugs crystal in a plaster body layer does not advance quickly since it is late, but crystallization of drugs

advances in a plaster body layer gradually. It is hard to say that the pharmaceutical preparation with which some drugs in the inside of a plaster body layer exist by the crystallized state turns into pharmaceutical preparation which may have a problem at the stability of quality and was not necessarily excellent in percutaneous absorption, the durability of drug effect, and a skin adhesive property by containing drugs by the concentration more than the saturation solubility to a binder as mentioned above.

[0006]

[Means for Solving the Problem] As a result of repeating research wholeheartedly in view of the above actual condition, this invention persons succeeded in obtaining the percutaneous absorption mold pharmaceutical preparation which tulobuterol is dissolving into a plaster body layer by 5% of the weight or more of high concentration.

[0007] That is, this invention is (1). Percutaneous absorption mold pharmaceutical preparation which the plaster body layer containing tulobuterol and a binder is the percutaneous absorption mold pharmaceutical preparation which comes to carry out a laminating to a base material, and is characterized by tulobuterol containing 5% of the weight or more in the state of the dissolution in this plaster body layer.

(2) The above whose binder is an acrylic binder or a rubber system binder (1) Percutaneous absorption mold pharmaceutical preparation of a publication.

(3) The above containing the polymer with which an acrylic binder comes to carry out the polymerization of the acrylic-acid alkyl ester whose carbon numbers of an alkyl group are 4-12 (meta) at 50% of the weight or more of a rate (2) Percutaneous absorption mold pharmaceutical preparation of a publication.

(4) The above containing the copolymer with which an acrylic binder comes to copolymerize the functionality monomer which has acrylic-acid alkyl ester whose carbon numbers of an alkyl group are 4-12 (meta) 60 to 98% of the weight, and has at least one partial saturation double bond in intramolecular, and has a functional group in a side chain at 2 - 40% of the weight of a rate (2) Percutaneous absorption mold pharmaceutical preparation of a publication.

(5) The above which is the radical chosen from the group which the functional group of a functionality monomer becomes from a carboxyl group, hydroxyl, a sulfonic group, the amino group, an amide group, an alkoxyl group, a cyano group, and an acyloxy radical (4) Percutaneous absorption mold pharmaceutical preparation of a publication.

(6) The above which is the monomer chosen from the group which a functionality monomer becomes from acrylic-acid (meta) and acrylic-acid (meta) 2-hydroxyethyl ester, a styrene sulfonic acid, acrylamide (meta), vinyl pyrrolidone, acrylic-acid (meta) 2-aminoethyl ester, acrylonitrile, acrylic-acid (meta) 2-methoxy ethyl ester, and vinyl acetate (4) Percutaneous absorption mold pharmaceutical preparation of a publication.

(7) The above whose rubber system binder contains at least a kind of macromolecule chosen from a polyisobutylene and a styrene diene styrene block copolymer (2) Percutaneous absorption mold pharmaceutical preparation of a publication.

(8) The above which contains further a kind of additive chosen from the group which consists of polyoxyethylene alkyl ether with the ester of the fatty acid of carbon numbers 12-16, the monoglyceride of the fatty acid of carbon numbers 8-10, the ester of the dibasic acid of carbon numbers 6-10, and 2-5 addition mols, and polyoxyethylene alkyl phenyl ether with 2-5 addition mols five to 50% of the weight at least in a plaster body layer (1) - (7) Percutaneous absorption mold pharmaceutical preparation given in either.

[0008] As for the percutaneous absorption mold pharmaceutical preparation of this invention, high-concentration tulobuterol exists in a plaster body layer in the state of the dissolution. the pharmaceutical preparation of this invention be the percutaneous absorption mold pharmaceutical preparation with which it excelled also in the durability of the effect by carry out long duration maintenance of the effective blood drug concentration , and aging of adhesion physical properties , such as a skin adhesive property , be mitigated while it be excellent in the percutaneous absorption of drugs , especially the percutaneous absorption rate in the early stages of administration by hold tulobuterol in a plaster body layer in the condition of having dissolve completely , without a drugs crystal deposit also in high concentration .

[0009] In a plaster body layer, it dissolves in a binder and the tulobuterol used for the percutaneous absorption mold pharmaceutical preparation of this invention must exist in the state of the dissolution. If the tulobuterol in a plaster body layer exists by the crystallized state, the crystal of tulobuterol comes to deposit with time, and the skin adhesive property, percutaneous absorption, and drugs emission nature of pharmaceutical preparation change with time and are not desirable.

[0010] Here, when the crystal of tulobuterol views that tulobuterol exists in the state of the dissolution in a plaster body layer, or when it observes with an optical microscope, it is not observed, but I hear that a plaster body layer is uniform, and it is.

[0011] Conventionally, as that to which tulobuterol exists in the state of the dissolution in a plaster body layer, only 3 or less % of the weight of the thing was obtained, but 10% of the weight or more of the thing was preferably obtained 5% of the weight or more for the first time by this invention.

[0012] In this invention, the desired purpose is enough attained for the concentration of tulobuterol at 5 % of the weight or more among a plaster body layer.

[0013] Although it will not be limited especially if tulobuterol dissolves in a plaster body layer and the solubility becomes 5% of the weight or more of a thing as a binder contained in a plaster body layer, an acrylic binder and a rubber system binder are especially used suitably from points, such as a skin adhesive property.

[0014] The above-mentioned acrylic binder consists of an acrylic polymer, and the homopolymers of acrylic-acid (meta) alkyl ester or these copolymers are mentioned as the acrylic polymer concerned. With the alkyl in acrylic-acid (meta) alkyl ester here The straight chain or branched-chain alkyl of carbon numbers 4-12 is desirable. As such (meta) acrylic-acid alkyl ester Specifically Butyl acrylate (meta) ester, acrylic-acid (meta) t-butyl ester, Acrylic-acid pentyl ester, acrylic-acid (meta) hexyl ester, (Meta) Acrylic-acid heptyl ester, acrylic-acid (meta) octyl ester, (Meta) Acrylic-acid iso octyl ester, acrylic-acid (meta) nonyl ester, (Meta) (Meta) Acrylic-acid iso nonyl ester, acrylic-acid (meta) DESHIRU ester, acrylic-acid (meta) undecyl ester, acrylic-acid (meta) dodecyl ester, 2-ethylhexyl acrylate (meta) ester, etc. are mentioned. The polymerization of the acrylic-acid alkyl ester concerned (meta) is more preferably carried out at 60% of the weight or more of a rate 50% of the weight or more.

[0015] Moreover, one sort of the monomer indicated below to be the above-mentioned (meta) acrylic-acid alkyl ester or two sorts or more of copolymers can also be suitably used as an acrylic polymer used for this invention.

[0016] As this monomer, while ***** (ing) a partial saturation double bond at least to intramolecular the functionality monomer which has functional groups, such as a carboxyl group, hydroxyl, a sulfonic group, an amino group, an amide group, an alkoxyl group, a cyano group, and an acyloxy radical, in a side chain -- [-- for example The alkyl group of acrylic-acid alkyl ester The straight chain or branched-chain alkoxy group of carbon numbers 1-4 (Meta) On the alkoxy denaturation monomer {concrete target of the acrylic-acid (meta) alkyl ester (which for example, denaturalized by the methoxy group, the ethoxy radical, etc.) }], such as acrylic-acid 2-methoxy ethyl ester and acrylic-acid (meta) 2-ethoxyethyl ester, (Meta) Acrylonitrile, vinyl acetate, propionic-acid vinyl, vinyl pyrrolidone, Vinyl caprolactam, acrylic-acid (meta), and acrylic-acid (meta) 2-hydroxyethyl ester, a styrene sulfonic acid, acrylamide (meta), acrylic-acid (meta) 2-aminoethyl ester, etc. are mentioned.

[0017] When using the copolymer which consists of acrylic-acid (meta) alkyl ester and the above-mentioned functionality monomer as the acrylic polymer concerned, it is desirable to carry out copolymerization of 65 - 97 % of the weight and the above-mentioned monomer for acrylic-acid (meta) alkyl ester at 3 - 35% of the weight of a rate preferably two to 40% of the weight 60 to 98% of the weight.

[0018] As a rubber system binder, the rubber system binder which consists of a polyisobutylene polybutene system, a styrene diene styrene block copolymer, a styrene butadiene system, a nitril system, a chloroprene system, a vinylpyridine system, a polyisobutylene system, a butyl system, an isoprene isobutylene system, etc. is mentioned, for example. Especially, from the soluble and skin adhesive point over tulobuterol, a polyisobutylene, a styrene diene styrene block copolymer (for example, [a styrene butadiene styrene block copolymer (SBS), a styrene isoprene styrene block copolymer (SIS), etc.] etc.), etc. are used preferably, and these may be mixed and used.

[0019] Moreover, in order to acquire moderate adhesion and drugs solubility, that from which average

molecular weight differs can be mixed and used for a rubber system binder of the same component or a different component. For example, when a polyisobutylene is mentioned as an example and explained, the mixture of the polyisobutylene of the amount of giant molecules of mean molecular weights 300,000–2,500,000, and the polyisobutylene of the inside molecular weight of mean molecular weights 10,000–200,000 and/or the polyisobutylene of the low molecular weight of mean molecular weights 500–4,000 is desirable. It is suitable to blend the polyisobutylene of inside molecular weight for the polyisobutylene of the amount of giant molecules, and to blend the polyisobutylene of low molecular weight at 10 – 60% of the weight of a rate zero to 80% of the weight ten to 80% of the weight zero to 90% of the weight 20 to 50% of the weight preferably ten to 80% of the weight here. [0020] The average molecular weight in this invention is Flory. It is the viscosity average molecular weight calculated from a viscosity formula.

[0021] In order to give moderate adhesiveness, tackifiers, such as rosin system resin, polyterpene resin, coumarone-indene resin, petroleum system resin, terpene-phenol resin, and xylene resin, may be blended with the rubber system binder concerned. A tackifier can blend preferably these one sorts or two sorts or more at 5 – 40% of the weight of a rate 50 or less % of the weight to a rubber system binder.

[0022] In this invention, the solubility of the tulobuterol in the inside of a plaster body layer can be raised further, and the additive as a dissolution assistant can be blended into a plaster body layer so that further high-concentration tulobuterol can be held in the condition of having dissolved completely. The additive to blend is excellent in compatibility with a binder, and fully dissolves tulobuterol. That what is necessary is just what is not made to produce separation with a binder component and an additive with time, but has a bad influence neither on an adhesion property nor emission nature. For example, the ester of the fatty acid of carbon numbers 12–16, the monoglyceride of the fatty acid of carbon numbers 8–10, At least one sort chosen from polyoxyethylene alkyl ether with 2–5 addition mols and polyoxyethylene alkyl phenyl ether with 2–5 addition mols as the ester of the dibasic acid of carbon numbers 6–10 and a nonionic surface active agent can be used.

[0023] As ester of the fatty acid of the above-mentioned carbon numbers 12–16, ester with C1 of C12 – C16 fatty acids, such as lauric-acid (C12) hexyl, myristic-acid (C14) isopropyl, and palmitic-acid (C16) isopropyl, – C10 alkyl etc. is specifically mentioned.

[0024] As a monoglyceride of the fatty acid of the above-mentioned carbon numbers 8–10, the monoglyceride of C8, such as caprylic-acid (C8) monoglyceride and capric-acid (C10) monoglyceride, – C10 fatty acid etc. is specifically mentioned.

[0025] As ester of the dibasic acid of the above-mentioned carbon numbers 6–10, ester with the JI (C1 – C10) alkyl of C6, such as adipic-acid (C6) diisopropyl, dioctyl adipate, and sebacic-acid (C10) diethyl, – C10 dibasic acid etc. is specifically mentioned.

[0026] As polyoxyethylene alkyl ether with the 2–5 above-mentioned addition mols, and polyoxyethylene alkyl phenyl ether with 2–5 addition mols the carbon number of the alkyl group -- 6–18 -- desirable -- 8–12 -- it is -- as polyoxyethylene alkyl ether -- concrete -- the polyoxyethylene lauryl ether -- The polyoxyethylene oleyl ether, the polyoxyethylene cetyl ether, etc. are mentioned. As polyoxyethylene alkyl phenyl ether, the polyoxyethylene nonylphenyl ether, polyoxyethylene octyl phenyl ether, etc. are specifically mentioned.

[0027] Especially, polyoxyethylene octyl phenyl ether with 2–5 addition mols which are polyoxyethylene alkyl phenyl ether of the adipic-acid diisopropyl and 2–5 addition mols which are ester of the myristic-acid isopropyl which is ester of the fatty acid of carbon numbers 12–16, the caprylic-acid monoglyceride which is a monoglyceride of the fatty acid of carbon numbers 8–10, and the dibasic acid of carbon numbers 6–10 is desirable, and myristic-acid isopropyl is used more preferably.

[0028] As for this additive, it is desirable among a plaster body layer to be more preferably blended at 20 – 40% of the weight of a rate ten to 40% of the weight five to 50% of the weight. When the loadings of an additive are less than 5 % of the weight, there is an inclination it to become difficult to hold after more high-concentration tulobuterol has dissolved completely in a plaster body layer, conversely, when exceeding 50 % of the weight, the cohesive force of a plaster body layer declines and there is an inclination the paste remainder to a hide skin surface etc. becomes easy to produce at the time of exfoliation.

[0029] Moreover, when blending the above-mentioned additive with the binder which has a cross-linking functional group, it is desirable to perform bridge formation processing with a suitable bridge formation means. By performing bridge formation processing, a binder can be in the so-called gel state, can suppress the outflow of the additive component to contain, and can give moderate cohesive force to a plaster body layer. The chemical bridge formation processing using cross linking agents, such as physical bridge formation according [crosslinking reaction] to radiation irradiation, such as UV irradiation and electron beam irradiation, the poly isocyanate compound, organic peroxide, an organic metal salt, a metal alcoholate, metal chelate compound, and a polyfunctional compound, etc. is used.

[0030] In order to make the paste remainder to the hide skin surface at the time of exfoliation removal hard to be equal to pasting of the long duration to a hide skin surface, and to produce, the thickness of the plaster body layer containing an above-mentioned binder and tulobuterol has desirable 20–100 micrometers, and its 20–50 micrometers are more desirable.

[0031] Especially if the plaster body layer containing tulobuterol can be formed and supported on the one side as a base material used for the percutaneous absorption mold pharmaceutical preparation of this invention, it will not be limited, but when that to which tulobuterol does not usually shift substantially is used and it sticks especially on a hide skin surface, what has the moderate flexibility which can follow a curve and a motion of a hide skin surface in extent which does not produce remarkable sense of incongruity is desirable.

[0032] Specifically, the monolayer films which consist of metallic foils, such as plastic film, such as a polyethylene system, a polypropylene system, a polyester system, a polyvinyl acetate system, ethylene / vinyl acetate copolymer, a polyvinyl chloride system, and a polyurethane system, aluminium foil, and tinfoil, a nonwoven fabric, textile fabrics, paper, etc., or these laminated films can be used.

[0033] 5–500 micrometers of thickness of a base material are usually 5–200 micrometers preferably. Moreover, as for these base materials, it is desirable to perform corona discharge treatment, plasma treatment, oxidation treatment, etc. to the field where the laminating of the plaster body layer is carried out in order to raise adhesion with a plaster body layer, and anchoring nature.

[0034] Especially the manufacture approach of the percutaneous absorption mold pharmaceutical preparation of this invention is not limited, for example, tulobuterol and a binder are completely dissolved in organic solvents, such as ethyl acetate, a hexane, and toluene, and the method of applying the obtained solution to one side of a base material, drying and making a plaster body layer form on the surface of a base material etc. is mentioned. Moreover, the above-mentioned solution is applied on the mold release liner for protection, it can dry, a plaster body layer can be made to be able to form on a mold release liner, and it can manufacture also by pasting up a base material on a plaster body layer after it.

[0035] As for the percutaneous absorption mold pharmaceutical preparation of this invention, it is desirable to cover and protect the exposure of a plaster body layer at a mold release liner ***** [just before sticking to a hide skin surface], in order that a plaster body layer may prevent to paste an instrument, a container, etc. in vain during manufacture, conveyance, or preservation, and in order to prevent degradation of pharmaceutical preparation. And this is exfoliated at the time of use, the field of a plaster body layer is exposed, and the skin is stuck and medicated.

[0036] The laminate film of the papers, such as films, such as polyester, a polyvinyl chloride, a polyvinylidene chloride, and polyethylene terephthalate, paper of fine quality, and glassine, the paper of fine quality or glassine, and polyolefine with which exfoliation processing was performed etc. is used by applying silicone resin, a fluororesin, etc. to the field which will not be restricted especially if it exfoliates easily from a plaster body layer as a mold release liner at the time of use, for example, contacts a plaster body layer.

[0037] 12–200 micrometers of thickness of a mold release liner are usually 50–100 micrometers preferably.

[0038] The dose of the percutaneous absorption mold pharmaceutical preparation of this invention is the pharmaceutical preparation concerned which usually contained 0.1–5mg of tulobuterol per time to the adult although it changed with a patient's age, weight, symptoms, etc. 1–50cm of skins 2 It will stick about once on 1 time – the 2nd on the 1st.

[0039]

[Example] Although an example and the example of an experiment are hereafter shown in order to explain this invention to a detail, this invention is not limited at all by these. In addition, in the following examples, the section and % mean weight section and weight %, respectively.

[0040] Under the example 1 inert-gas ambient atmosphere, the polymerization of the 2-ethylhexyl acrylate ester 50 section, the acrylic-acid 2-methoxy ethyl ester 25 section, and the vinyl acetate 25 section was carried out in ethyl acetate, and the acrylic binder solution was prepared. After adding and mixing and fully stirring so that the loadings to the inside of a plaster body layer may become 10% in this solution about tulobuterol, it applied and dried and the plaster body layer was formed so that the thickness after drying on a mold release liner might be set to 40 micrometers. Next, the percutaneous absorption mold pharmaceutical preparation of lamination and this invention was obtained for the plaster body layer to the base material (polyester film with a thickness of 12 micrometers).

[0041] After adding and mixing and fully stirring polyoxyethylene octyl phenyl ether (three addition mols of oxyethylene, OP-3, product made from NIKKORU) as tulobuterol and an additive in the acrylic binder solution obtained in the example 2 example 1 so that the loadings to the inside of a plaster body layer may become 10%, respectively, the percutaneous absorption mold pharmaceutical preparation of this invention was obtained like the example 1.

[0042] Under the example 3 inert-gas ambient atmosphere, the polymerization of the 2-ethylhexyl acrylate ester 95 section and the acrylic-acid 5 section was carried out in ethyl acetate, and the acrylic binder solution was prepared. It adds so that the loadings to the inside of a plaster body layer may become 20% and 30% in this solution about myristic-acid isopropyl as tulobuterol and an additive, respectively. It mixes and is the poly isocyanate compound (it coronate-HL(s)) as a cross linking agent further. After adding and mixing and fully stirring Japanese polyurethane company make so that it may become 0.15% to an acrylic binder, it applied and dried and the plaster body layer was formed so that the thickness after drying on a mold release liner might be set to 60 micrometers. Next, the percutaneous absorption mold pharmaceutical preparation of lamination and this invention was obtained for the plaster body layer to the nonwoven fabric side of a base material (the nonwoven fabric made from polyester of metsuke amount 12 g/m², and laminated film of polyester film with a thickness of 6 micrometers). In addition, in order to advance crosslinking reaction, after sticking a base material, it heated at 70 degrees C for 60 hours.

[0043] After adding and mixing and fully stirring myristic-acid isopropyl and a caprylic-acid monoglyceride as tulobuterol and an additive in the acrylic binder solution obtained in the example 4 example 3 so that the loadings to the inside of a plaster body layer may become 10%, 40%, and 5%, respectively, the percutaneous absorption mold pharmaceutical preparation of this invention was obtained like the example 3.

[0044] The example 5 polyisobutylene (VISTANEX MML-140, Exxon chemistry company make) 50 section, the polyisobutylene (HIMOL 6H, Nippon Oil chemistry company make) 30 section, and the alicycle group system petroleum resin (made in [Arakawa chemistry company] 100 degrees-C [of softening temperatures] and Al Cong P-100) 20 section were dissolved in the hexane, and the rubber system polymer solution was prepared. After adding and mixing and fully stirring myristic-acid isopropyl as tulobuterol and an additive in this solution so that the loadings to the inside of a plaster body layer may become 5% and 40%, respectively, it applied and dried and the plaster body layer was formed so that the thickness after drying on a mold release liner might be set to 40 micrometers. Next, the percutaneous absorption mold pharmaceutical preparation of lamination and this invention was obtained for the plaster body layer to the nonwoven fabric side of a base material (the nonwoven fabric made from polyester of metsuke amount 12 g/m², and laminated film of polyester film with a thickness of 6 micrometers).

[0045] After adding and mixing and fully stirring adipic-acid diisopropyl as tulobuterol and an additive to the rubber system polymer solution obtained in the example 6 example 5 so that the loadings to the inside of a plaster body layer may become 5% and 30%, respectively, the percutaneous absorption mold pharmaceutical preparation of this invention was obtained like the example 5.

[0046] The example 7 styrene butadiene styrene block-copolymer (SBS) (styrene/butadiene = 30/70 (weight ratio), Cariflex TR-1101, shell chemistry company make) 80 section and the alicycle group

system petroleum resin (105 degrees-C [of softening temperatures], S KORETTSU 5300, Exxon chemistry company make) 20 section were dissolved in toluene, and the rubber system polymer solution was prepared. After having added, having mixed myristic-acid isopropyl as tulobuterol and an additive in this solution so that the loadings to the inside of a plaster body layer might become at 5% and 40%, respectively, and fully stirring, the percutaneous absorption mold pharmaceutical preparation of this invention was obtained like the example 5.

[0047] The example 8 styrene isoprene styrene block-copolymer (SIS) (styrene/isoprene = 14/86 (weight ratio), Cariflex TR-1107, shell chemistry company make) 70 section, the polyisobutylene (HIMOL 4H, Nippon Oil chemistry company make) 10 section, and the alicycle group system petroleum resin (made in [Arakawa chemistry company] 100 degrees-C [of softening temperatures] and Al Cong P-100) 20 section were dissolved in toluene, and the rubber system polymer solution was prepared. After having added, having mixed myristic-acid isopropyl as tulobuterol and an additive in this solution so that the loadings to the inside of a plaster body layer might become at 5% and 40%, respectively, and fully stirring, the percutaneous absorption mold pharmaceutical preparation of this invention was obtained like the example 5.

[0048] Percutaneous absorption mold pharmaceutical preparation was obtained like the example 1 except having used the acrylic binder solution which was made to carry out the polymerization of the tridecyl acrylate ester 45 section, the acrylic-acid 2-methoxy ethyl ester 25 section, and the vinyl acetate 30 section under an inert gas ambient atmosphere and in ethyl acetate, and was obtained instead of the acrylic binder solution of example of comparison 1 example 1. In addition, in the plaster body layer of this pharmaceutical preparation, the crystal of tulobuterol was distributing by viewing or microscope observation.

[0049] Percutaneous absorption mold pharmaceutical preparation was obtained like the example 5 except having used the rubber system polymer solution obtained by dissolving the polyisoprene (IR2200, Japan Synthetic Rubber Co., Ltd. make) 70 section and the alicycle group system petroleum resin 30 section in a hexane instead of the rubber system polymer solution of example of comparison 2 example 5. In addition, in the plaster body layer of this pharmaceutical preparation, the crystal of tulobuterol was distributing by viewing or microscope observation.

[0050] The presentation of the plaster body layer of the percutaneous absorption mold pharmaceutical preparation obtained in examples 1-8 and the examples 1-2 of a comparison is shown in Table 1.

[0051]

[Table 1]

		粘着剤	添加剤	薬剤含量	薬剤の状態
実施例	1	アクリル系共重合体	なし	10%	溶解
	2	アクリル系共重合体	ポリオキシエチレンオキチル フェニルエーテル 10%	10%	溶解
	3	アクリル系共重合体	ミリスチン酸イソプロピル 30%	20%	溶解
	4	アクリル系共重合体	ミリスチン酸イソプロピル 40% カプリル酸モノグリセリド 5%	10%	溶解
	5	ゴム系高分子 (ポリイソブレン)	ミリスチン酸イソプロピル 40%	5%	溶解
	6	ゴム系高分子 (ポリイソブレン)	アジピン酸イソプロピル 30%	5%	溶解
	7	ゴム系高分子 (SBS)	ミリスチン酸イソプロピル 40%	5%	溶解
	8	ゴム系高分子 (SIS/ポリイソブレン)	ミリスチン酸イソプロピル 40%	5%	溶解
比較例	1	アクリル系共重合体	なし	10%	結晶分散
	2	ゴム系高分子 (ポリイソブレン)	ミリスチン酸イソプロピル 40%	5%	結晶分散

[0052] Stability of adhesion physical properties (adhesive strength) with the passage of time was examined about the percutaneous absorption mold pharmaceutical preparation obtained in example of experiment 1 examples 1-8, and the examples 1-2 of a comparison, and the percutaneous absorption mold pharmaceutical preparation which saved this for one month at 40 degrees C.

[0053] After sticking each band-like sample judged in width of face of 12mm on a <adhesive strength test-method> bakelite plate, making the roller of 850g of loads (it is 300g about examples 3 and 4) restored once, making it stick and leaving it, under the conditions of 23 degrees C and 60%RH The tensile load when exfoliating the rate for 300mm/in the direction of 180 degrees was measured using the tension tester (SHOPPA mold tension tester: the Kamishima factory company make). A result is shown in Table 2.

[0054]

[Table 2]

		接着力 (g/12mm)	
		初期	40℃、1ヶ月
実施例	1	546	554
	2	413	408
	3	78	82
	4	66	63
	5	48	52
	6	58	55
	7	61	58
	8	64	60
比較例	1	519	364
	2	57	21

[0055] The pharmaceutical preparation of examples 1-8 showed the adhesion property more stable than the first stage, and change of adhesive strength with time was not accepted. As for the pharmaceutical preparation of the examples 1-2 of a comparison, the fall of the adhesive strength by which a drugs crystal deposit with time in a plaster body layer is considered to be the cause was accepted to it.

[0056] The 2nd law [in / pharmaceutical preparation / which saved this for one month at 40 degrees C / the percutaneous absorption mold pharmaceutical preparation obtained in example of experiment 2 examples 1 and 5 and the examples 1 and 2 of a comparison and / percutaneous absorption mold / General Test Procedures of a Japanese pharmacopoeia] of a dissolution test examined stability of the drugs emission nature out of pharmaceutical preparation with the passage of time. A result is shown in Table 3.

[0057] The <elution test approach> elution test machine : NTR-V36 (Toyama industrial incorporated company)

Sample size: 10cm 2 test fluid : Distilled water, 32 degrees C, 500ml paddle rotational frequency : 50 revolution-per-minute measuring methods : Ultraviolet spectroscopy extinction method (211nm)

[0058]

[Table 3]

		放 出 率 (%)					
		初期			4 0 ℃、1 ヶ月		
		3 h r	8 h r	24 h r	3 h r	8 h r	24 h r
実施例	1	62.1	91.4	98.6	60.9	91.2	98.2
	5	47.6	74.7	93.9	45.8	75.3	95.1
比較例	1	54.7	82.1	96.2	35.3	53.6	81.0
	2	39.8	56.4	82.3	30.1	45.3	72.2

[0059] The pharmaceutical preparation of examples 1 and 5 showed drugs emission nature more stable than the first stage, and change of the drugs emission nature in preservation with the passage of time was not accepted. As for the pharmaceutical preparation of the examples 1 and 2 of a comparison, the fall of the drugs emission nature by which a drugs crystal deposit with time in a plaster body layer is considered to be the cause was accepted to it.

[0060] It applied behind the rabbit which carried out depilating of the percutaneous absorption mold pharmaceutical preparation obtained in example of experiment 3 examples 1 and 5, and the examples 1 and 2 of a comparison, and blood-drug-concentration transition of the tulobuterol after application was considered. A result is shown in drawing 1.

[0061] <Blood-drug-concentration test-method> sample size: 10cm² pasting part : Rabbit regions-of-back pasting time amount which carried out depilating : 24 hour blood-drug-concentration measuring method: Gas chromatography (electron capture ionization detector)

[0062] The start and durability of blood drug concentration in the early stages of application were excellent in the pharmaceutical preparation of examples 1 and 5. Although the pharmaceutical preparation of the examples 1 and 2 of a comparison was excellent in durability to it, the start of the blood drug concentration in the first stage was not a satisfying thing.

[0063]

[Effect of the Invention] while the percutaneous absorption mold pharmaceutical preparation of this invention be hold in a plaster body layer where the tulobuterol which be a drug effect component be completely dissolved by high concentration, and no aging of the drugs emission nature accompanying a drugs crystal deposit with time or an adhesion physical properties be and excel in the percutaneous absorption of drugs, especially the percutaneous absorption rate in the early stages of administration, it excel also in the durability of the effect by carry out the long duration maintenance of the effective blood drug concentration, and aging of adhesion physical properties, such as a skin adhesive property, be mitigate.

[Translation done.]

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DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]

[Drawing 1] Drawing 1 is a graph which shows aging of the blood drug concentration of the tulobuterol in the example 3 of an experiment.

[Translation done.]

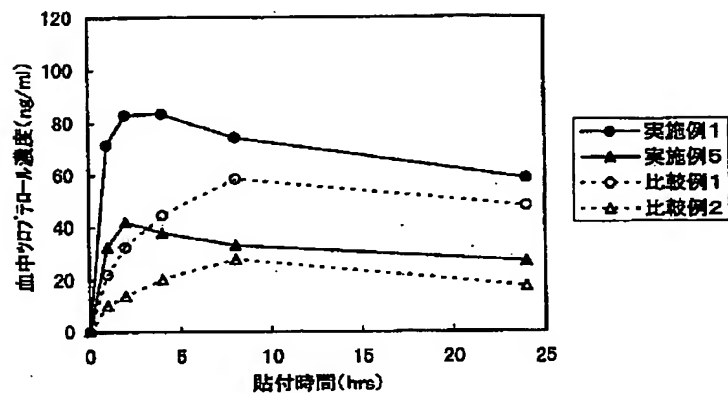
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DRAWINGS

[Drawing 1]



[Translation done.]